CHRONIC TOXICITY SUMMARY

SELENIUM AND SELENIUM COMPOUNDS

(other than Hydrogen Selenide**)**

Molecular Formula	*Synonyms*	*Molecular Weight* (g/mol)	*CAS Reg. No.*
Se	elemental selenium	78.96	7782-49-2
SeO_2	selenium dioxide; selenium oxide; selenious anhydride	110.96	7446-08-4
H_2SeO_3	selenious acid	128.97	7783-00-8
$SeOCl_2$	seleninyl chloride; selenium oxychloride; selenium oxichloric	165.86	7791-23-3
Na_2SeO_3	disodium selenite	263.01	10102-18-8
Na_2SeO_4	disodium selenate	188.94	13410-01-0
SeS	selenium sulfide; sulfur selenide	111.02	7446-34-6

I. Chronic Toxicity Summary

Inhalation reference exposure level **20 µg/m^3**
Oral reference exposure level **0.005 mg/kg/day** (USEPA RfD)
Critical effect(s) Clinical selenosis
Hazard index target(s) Alimentary system; cardiovascular system; nervous system

II. Chemical Property Summary (HSDB, 1995; Weast, 1980; Canady and Hodes, 1994; ACGIH, 1992)

Description	Se^0 crystal: metallic gray H_2SeO_4, Na_2SeO_3: white crystals H_2SeO_3, Na_2SeO_4: colorless crystals SeO_2: lustrous crystals; yellow vapor SeS: yellow to orange powder
Molecular formula	see above
Molecular weight	see above
Vapor pressure	0.001 torr @ 20°C
Melting point	SeO_2: 340°C SeS: decomposes at 118-119°C
Solubility	Se^0: insoluble in water, alcohol; slightly soluble in CS_2; soluble in ether H_2SeO_4: sol. in water; decomposes in alcohol H_2SeO_3: sol. in hot water, alcohol Na_2SeO_3: sol. in water Na_2SeO_4: 84 g/100 ml water at 35°C SeO_2: 38.4 g/100 ml water at 14°C SeS: insoluble in water
Conversion factor	Se^0: not applicable (particulate) SeO_2: 4.5 µg/m^3 per ppb at 20°C

III. Major Uses and Sources

Selenium occurs in four valence states: selenates (Se^{6+}), selenites (Se^{4+}), selenides (Se^{2-}), and elemental selenium (Se^0) (Goyer, 1991) which include compounds formed with oxygen, sulfur, metals, and/or halogens. Selenium compounds are used in the glass industry as decolorizing agents and in the rubber industry as vulcanizing agents. Selenium compounds are also found in toning baths used in photography and xerography, and in insecticides and photoelectric cells. Selenious acid is a component of gun cleaning chemicals (Quadrani *et al*., 2000). Selenium sulfide is used in shampoos as an anti-dandruff agent. The most widely used selenium compound in industry is selenium dioxide (SeO_2) which catalyzes reactions of organic compounds and is produced by the oxidation of selenium with nitric acid followed by evaporation or by burning selenium in oxygen (HSDB, 1995). The largest anthropogenic sources of atmospheric selenium are from the combustion of fossil fuels and the production/refining of copper; particulates are the primary expected form of the compound (National Academy of Sciences (NAS), 1976; U.S. EPA, 1984). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 12,417 pounds of selenium and 4846 pounds of selenium sulfide (CARB, 1999).

Selenium is an essential trace element in humans and other species; selenium deficiency leads to cardiomyopathy in humans (Goyer, 1991). For dietary intake, the National Research Council has

set a U.S. Recommended Daily Allowance (RDA) of 0.87 μg/kg (55-70 μg/person/day) (Subcommittee on the Tenth Edition of the RDAs, 1989). The average daily oral intake of selenium is 125 μg/person (U.S. EPA, 1991). Organic selenium compounds (e.g., dimethyl selenide) are known to occur as metabolites and as microbial degradation products in the environment. These compounds appear to have relatively low toxicity.

IV. Effects of Human Exposures

Acute occupational exposure to SeO_2 resulted in bronchospasm, irritation of the upper respiratory passages, violent coughing, and gagging with nausea and vomiting (Wilson, 1962).

The relationship between inhalation exposure to selenium and the presence of selenium in the urine was investigated in a five year study of workers at a selenium rectifying plant (Glover, 1967). Workers were exposed to fumes and dusts of elemental red selenium, which, the author reported, is converted 80% to SeO_2 in the presence of air. Average air concentrations of selenium were reported to be 3.6 mg/m^3 in grinding processes, 0.04 mg/m^3 in annealing processes, and a range of averages of 0.23-0.87 mg Se/m^3 in various "special" processes, e.g., punching, scraping, sorting, refining, and testing. The same author previously reported symptoms among selenium exposed workers including garlic-like odor of the breath, skin rashes, indigestion, and poorly-defined "socio-psychological" effects including lassitude and irritability (Glover, 1954).

Clinical signs of toxicity were observed among a population exposed to high levels of selenium in soils and food supplies in China (Yang *et al.*, 1983). Approximately half of 248 people in this region showed symptoms including hair and nail loss, discoloration and decay of the teeth, and CNS disturbances including pain and anesthesia of the extremities. Animals in the region were also affected, with hoof damage and horn sloughing reported in water buffalo, cattle, and pigs. Populations in low-, medium-, and high-selenium areas of China were later studied to associate the symptoms with selenium intake. Estimated daily intake for adults in these areas were 70, 195, and 1438 μg Se for males and 62, 198, and 1238 μg for females, respectively (Yang *et al.*, 1989). Selenium intake was highly correlated with whole blood, breast milk, and 24-hour urine selenium levels. The authors also suggested the possibility of liver dysfunction as indicated by a delay in prothrombin time among persons with intake of 750-850 μg Se/day. More clearly recognized and characteristic clinical signs, however, were only observed in a group exposed to greater than 1261 μg Se/day and not among those exposed to less than 853 μg Se/day. Assuming a 55 kg body weight, these respective daily dose rates were 0.023 and 0.015 mg/kg-day.

A population of 142 subjects in seleniferous areas of western South Dakota and eastern Wyoming was examined for signs of selenosis over a two-year period with monitoring of selenium levels in diet, whole blood, serum, urine, and toenails (Longnecker *et al.*, 1991). Subjects completed health questionnaires, underwent physical examinations, provided blood samples for clinical assessment, and provided blood, urine, toenails, and duplicate-plate food collections for selenium analysis. About half of the 142 free-living subjects had selenium intakes greater than 2.54 mμmol/day (200 μg/day) (range 0.86-9.20 mμmol/day, or 68-724 μg/day). Average intake among the population was estimated at 239 μg Se/day. No clinical

signs and no changes in hematological function, clinical chemistry, or liver function were observed in the population, even in subjects whose intake was as high as 9.20 mμmol/day (724 μg/day).

V. Effects of Animal Exposures

Toxic effects from acute inhalation exposure to selenium dust were examined in rats, guinea pigs, and rabbits (Hall *et al.*, 1951). Twenty female rats were exposed once for 8 hours to 33 ± 10 mg Se/m^3. Many animals showed signs of pulmonary effects at both one week and 4 weeks after exposure; however, no control group was included in the experiment with which to compare incidence. Similarly, six female rabbits and 10 male guinea pigs were exposed to the same level of selenium dust for four 4-hour periods every 48 hours (8 days total duration). The animals showed signs of interstitial pneumonitis at one week (2 animals of each species) and lung congestion and alveolar infiltration of large macrophages.

Guinea pigs exposed one time to concentrations "less than 0.021 mg H_2Se/L" (22 mg Se/m^3 as hydrogen selenide) for 2, 4, or 8 hours exhibited difficulty breathing and a red-tinged discharge from the nose (Dudley and Miller, 1941). Mortality studies were conducted with guinea pigs (16/group) using the same exposure duration and selenium concentrations ranging from 1 to 43 mg Se/m^3. Fifty percent mortality was observed at 30 days among animals exposed once for 2 hours to 12 mg Se/m^3. Mortality after 30 days was 50% among animals exposed once to 1 mg Se/m^3 for 8 hours. Histopathological evaluation of guinea pigs exposed once for 4 hours to 8 mg Se/m^3 showed fatty change to the liver, pneumonia, lymphoid hyperplasia, and increased reticuloendothelial tissue in the spleen. These effects did not begin to resolve until more than 17 days after the exposure.

Several studies have addressed the toxicity of selenium compounds to animals when administered in either food or drinking water. Mice (50/group) treated with 0, 1, 4, or 8 ppm Na_2SeO_3 in drinking water over 50 weeks showed decreased growth rates at 8 ppm (Jacobs and Forst, 1981). The same group reported gross liver pathology in male mice treated by oral gavage for 3 days with 0.5 ml of 64 ppm Na_2SeO_3. Hamsters (8/sex/group) treated with 0.1 (unsupplemented), 1, 5, 10, or 20 ppm Na_2SeO_3 in the diet for 42 days showed histopathological changes to the liver (Beems and van Beek, 1985). Rats (6-8/group) treated in the diet with SeS_2, Na_2Se, Na_2SeO_3, or Na_2SeO_4 showed increased relative liver weights and/or decreased body weight gain at 10 ppm (for each compound) over a 5 week exposure (Dausch and Fullerton, 1993). A 13-week drinking water study of Na_2SeO_3, and Na_2SeO_4 in rats and mice showed increased mortality, decreased body weights, and histopathological changes to the kidneys in rats and decreased body weight and decreased water consumption in mice (Abdo, 1994). Decreased body weights were observed in rats treated for 6 weeks in drinking water with 2 ppm Na_2SeO_3 or Na_2SeO_4 (Palmer and Olson, 1974).

Decreased percentage of live spermatozoa, altered sperm morphology, and decreased body weight gain were observed in rats (6/group) treated for 5 weeks with 2 ppm Na_2SeO_3 in the diet (Kaur and Parshad, 1994). Rats (7-12/group) exposed to 0, 4, 8, or 16 ppm Na_2SeO_3 in drinking

water for 240 days showed alterations in testicular LDH and β-glucuronidase activity at 4 ppm (Nebbia *et al.*, 1987).

Developmental toxicity endpoints were examined in hamsters (5-10/group) exposed by oral gavage on gestational day 8 to Na_2SeO_3 and Na_2SeO_4 at concentrations ranging from 0 - 110 μmol/kg body weight (Ferm *et al.*, 1990). Effects observed at 100 μmol Na_2SeO_3/kg included decreased fetal crown-rump length and increased percentage of abnormal litters. At 90 μmol Na_2SeO_4/kg, an increased percentage of abnormal litters was observed. Mice (10 or 14/group) treated with 0, 3, or 6 ppm Na_2SeO_3 in drinking water from 30 days pre-gestation through gestation showed altered estrus cycle length, decreased fetal growth, and a decreased number of ossified vertebrae in offspring (Nobunaga *et al.*, 1979).

VI. Derivation of Chronic Reference Exposure Level (REL) (for selenium and selenium compounds other than hydrogen selenide)

Study	Yang *et al*., 1989
Study population	400 people in China
Exposure method	Low, medium, & high environmental levels of Se
Critical effects	Clinical selenosis (liver, blood, skin, CNS)
LOAEL	0.023 mg/kg-day* (1.261 mg/day / 55 kg)
NOAEL	0.015 mg/kg-day* (0.853 mg/day / 55 kg)
Exposure continuity	Continuous
Exposure duration	Lifetime
Average experimental exposure	70, 195, and 1438 μg/day for adult males; 62, 198, and 1238 μg/day for adult females
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies factor	1
Intraspecies factor	3
Cumulative uncertainty factor	3
Oral reference exposure level	0.005 mg/kg/day (USEPA RfD)
Inhalation extrapolation factor	3,500 $\mu g/m^3$ per mg/kg-day
Inhalation reference exposure level	20 $\mu g/m^3$

*Factors: NOAEL (0.853 mg/day) and LOAEL (1.261 mg/day) calculated from regression analysis (log Y = 0.767 log X - 2.248, where Y = blood selenium and X = selenium intake) based upon the correlation (r = 0.962) between dietary selenium intake and blood selenium level for data showing incidence of clinical selenosis in adults based on an average adult body weight of 55 kg.

The inhalation chronic REL is based on the oral chronic REL, which is the same as the USEPA's oral reference dose (RfD) (U.S. EPA, 1996). In addition to being inhaled, airborne selenium can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for selenium is also required for Air Toxics Hot Spots health risk assessments. The chronic inhalation REL was derived by route-to-route extrapolation of the RfD. The

principal study used for the REL/RfD was that of Yang *et al*. (1989). Yang *et al*. (1989), in a follow-up to an earlier study (Yang *et al*., 1983), studied a population of approximately 400 individuals living in an area of China with unusually high environmental concentrations of selenium (Se). The subjects were evaluated for clinical and biochemical signs of Se intoxication. Three geographical areas with low, medium, and high selenium levels in the soil and food supply were chosen for comparison in the studies. The earlier study was conducted in response to endemic selenium intoxication in two separate areas with sample sizes of only 6 and 3. Comparisons were then made to a selenium-adequate area (n=8) and low-selenium area (n=13). The Yang *et al*. (1989) studies provide a much larger sample size and include additional analysis of tissue selenium levels. This allows a more accurate estimation of the dose-response relationship observed for selenium toxicity. Selenium levels in soil and approximately 30 typical food types commonly eaten by the exposed population showed a positive correlation with blood and tissue Se levels. The daily average Se intakes, based on lifetime exposure, were 70, 195, and 1438 μg for adult males and 62, 198, and 1238 μg for adult females in the low-, medium- and high-selenium areas, respectively. Significant correlations, demonstrated between Se concentrations of various tissues, were used to estimate the minimal daily Se intake values that elicited various alterations in biochemical parameters indicative of possible Se-induced liver dysfunction (i.e., prolongation of clotting time and serum glutathione titer) and clinical signs of selenosis (i.e., hair or nail loss, morphological changes of the nails, etc.). In this manner, a marginal safe level of daily Se intake was estimated. Analysis of the results indicated that persistent clinical signs of selenosis were observed only in 5/349 adults, a potentially sensitive subpopulation. The blood selenium concentration in this group ranged from 1.054 to 1.854 mg/L with a mean of 1.346 mg/L. Clinical signs observed included the characteristic "garlic odor" of excess selenium excretion in the breath and urine, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions, and CNS abnormalities (peripheral anesthesia, acroparesthesia, and pain in the extremities). Alterations in the measured biochemical parameters occurred at dietary intake levels of 750-850 μg/day. These alterations were described as a delay in prothrombin time, i.e., increase in blood coagulation time and reduction in blood glutathione concentration. However, these indicators were poorly characterized and are not typically used as an index for clinical selenosis resulting from chronic exposure to selenium (NAS, 1989). Based upon the blood selenium levels shown to reflect clinical signs of selenium intoxication, a whole blood selenium concentration of 1.35 mg/L corresponding to 1.261 mg of daily selenium intake is indicative of the lowest correlative selenium intake causing overt signs of selenosis. The next lowest whole blood selenium concentration of 1.0 mg/L, corresponding to 0.853 mg selenium/day, produces no clinical signs of selenosis. The NOAEL for this study is 0.85 mg Se/day and the LOAEL is 1.26 mg Se/day.

An intraspecies uncertainty factor of 3 was applied to the NOAEL to account for sensitive individuals. A full factor of 10 was not deemed necessary since similar NOAELs were identified in two moderately-sized human populations exposed to selenium levels in excess of the RDA throughout a lifetime without apparent clinical signs of selenosis. No modifying factor was applied by USEPA. OEHHA accepted the USEPA analysis.

Route-to-route extrapolation assumes by default that a chemical is equally absorbed by the inhalation and the oral routes and that the first pass effect due to metabolism by the liver is not important for the chemical. The latter assumption is applicable to most metals. There are

limited data to evaluate the assumption of equal absorption across the gastrointestinal tract and the lungs. Limited data indicate that 60% (range = 44-100%) of ingested Se is absorbed by the gastrointestinal tract, while in one study 30% (single estimate) of inhaled selenium was deposited in the respiratory tract (Owen, 1990). Deposition is dependent on particle size. The available data are not adequate to depart from the default assumption.

The USEPA stated its confidence in the RfD as: Study - Medium; Data Base - High; and RfD - High. Confidence in the chosen principal study is medium. Although this is a human epidemiological study in which a sizable population with sensitive subpopulations was studied, there are still several possible interactions that were not fully accounted for, e.g., fluoride intake and protein status. Also, except for clinical signs of selenosis there are no other reliable indicators, biochemical or clinical, of selenium toxicity. Confidence in the database is high because many animal studies and epidemiologic studies support the principal study. An additional human study with a freestanding NOAEL (Longnecker et al., 1991) provides support for the NOAEL identified in the principal study. Longnecker *et al*. (1991) found no effects at 238 µg Se per day, which would equate to 0.004 mg/kg-day for a 55 kg person. Therefore, high confidence in the RfD is selected based upon support of the critical study and the high level of confidence in the database.

There are insufficient data relating human inhalation exposure to selenium compounds to adverse health effects to use for the development of a chronic REL although toxicity has been reported from occupational exposure to gases of both H_2Se and SeO_2 (Buchan, 1947; Wilson, 1962). Experiments in animals have shown that H_2Se is toxic following inhalation exposure, with 8-hour exposures to concentrations as low as 1 mg H_2Se/m^3 causing "irritation sufficiently damaging to cause pneumonitis" and subsequently increasing 30-day mortality (Dudley, 1937; Dudley and Miller, 1941). Thus the selenium chronic REL is not meant to be applied to H_2Se, which may be considerably more toxic than other selenium compounds. At this time there are inadequate data to develop a REL for H_2Se. It is also not intended to be applied to organic metabolites of selenium.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the REL for selenium include its basis on a study with a large number of human subjects in a non-occupational setting that determined both a NOAEL and a LOAEL. The weaknesses include its basis on a route of exposure other than inhalation and its lack of applicability to hydrogen selenide, the most toxic selenium compound.

VIII. Potential for Differential Impacts on Children's Health

The key study (Yang *et al*., 1989) included evaluation of children as young as one year old. Thus the chronic REL should be protective of infants and children. No adverse reproductive outcomes were reported, although only 400 people were studied. However, the inhalation REL is based on an oral REL of 0.005 mg/kg-day (0.06 µmol/kg-day). Ferm *et al*. (1990) did not find

adverse effects on hamster development with Se doses below 34 μmol/kg. Thus the chronic REL should also be protective of infants and children.

IX. References

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